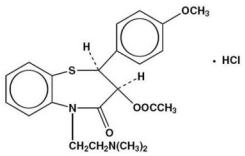
DILTIAZEM HYDROCHLORIDE - diltiazem hydrochloride tablet, film coated
Mylan Pharmaceuticals Inc.

Rx only

DESCRIPTION
Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5**H**)one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl), monohydrochloride, (+)-*cis*-. The structural formula is:



$C_{22}H_{26}N_2O_4S$ • HCl
M.W. 450.99
Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform.
Each tablet, for oral administration, contains 30 mg, 60 mg, 90 mg, or 120 mg diltiazem hydrochloride. In addition, each tablet contains the following inactive ingredients: ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, maltodextrin, polyethylene glycol, and sodium lauryl sulfate.
Diltiazem Hydrochloride Tablets, USP 30 mg, 60 mg, 90 mg and 120 mg meet *USP Dissolution Test 2*.

CLINICAL PHARMACOLOGY
The therapeutic benefits achieved with diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action
Although precise mechanisms of its antianginal actions are still being delineated, diltiazem is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm
Diltiazem has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by diltiazem.

2. Exertional Angina
Diltiazem has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects
Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.
In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given workload. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.
Intravenous diltiazem hydrochloride in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of diltiazem hydrochloride in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).
Chronic oral administration of diltiazem hydrochloride in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation.

Pharmacokinetics and Metabolism
Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. Diltiazem undergoes extensive metabolism in which 2% to 4% of the unchanged drug appears in the urine. *In vitro* binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown diltiazem binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Minimum therapeutic plasma levels of diltiazem appear to be in the range of 50 to 200 ng/mL. There is a departure from linearity when dose strengths are increased. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in AUC (area-under-the plasma concentration vs time curve) in the hepatically impaired patients. A single study in nine patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem as compared to patients with normal renal function.
Single oral doses of 30 to 120 mg of diltiazem tablets result in detectable plasma levels within 30 to 60 minutes and peak plasma levels 2 to 4 hours after drug administration. As the dose of diltiazem tablets is increased from a daily dose of 120 mg (30 mg qid) to 240 mg (60 mg qid) daily, there is an increase in area-under-the-curve of 2.3 times. When the dose is increased from 240 mg to 360 mg daily, there is an increase in area-under-the-curve of 1.8 times.

INDICATIONS AND USAGE
Diltiazem hydrochloride tablets are indicated for the management of chronic stable angina and angina due to coronary artery spasm.

CONTRAINDICATIONS
Diltiazem hydrochloride tablets are contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction
Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second-or-third-degree AV block (six of 1,243 patients or 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem. (See ADVERSE REACTIONS.)

2. Congestive Heart Failure
Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of diltiazem alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.

3. Hypotension
Decreases in blood pressure associated with diltiazem therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury
In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General
Diltiazem is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS) may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem undergoes bio-transformation by cytochrome P-450 mixed function oxidase. Coadministration of diltiazem with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

Beta-Blockers

Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem and beta-blockers is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of diltiazem concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro*, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine

A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, non-significant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis

Administration of diltiazem with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics

The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Cyclosporine

A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted or discontinued. The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine

Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40 to 72% increase) resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy

Teratogenic Effects

Pregnancy Category C
Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac abnormalities have usually been excluded.
In domestic placebo-controlled angina trials, the incidence of adverse reactions reported during diltiazem therapy was not greater than that reported during placebo therapy.
The following represent occurrences observed in clinical studies of angina patients. In many cases, the relationship to diltiazem has not been established. The most common occurrences from these studies as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%).
In addition, the following events were reported infrequently (less than 1%):
Cardiovascular: Angina, arrhythmia, AV block (first degree), AV block (second or third degree - see conduction warning), bradycardia, bundle branch block, congestive heart failure, ECG abnormality, flushing, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.
Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tremor.
Gastrointestinal: Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), thirst, vomiting, weight increase.
Dermatologic: Petechiae, photosensitivity, pruritus, urticaria.
Other: Amblyopia, CPK elevation, dry mouth, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties, tinnitus.
The following postmarketing events have been reported infrequently in patients receiving diltiazem: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia.
There have been observed cases of a generalized rash, some characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and diltiazem therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

OVERDOSAGE OR EXAGGERATED RESPONSE

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg.
The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases.
There have been 29 reports of diltiazem overdose in doses ranging from less than 1 g to 10.8 g. Sixteen of these reports involved multiple drug ingestions.
Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 g to 10.8 g. There were seven reports with fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine, as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure, and in cases of cardiac failure inotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.
In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences, the following measures may be considered:
Bradycardia: Administer atropine (0.60 to 1 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension: Vasopressors (e.g., dopamine or levarterenol bitartrate).
Actual treatment and dosage should depend on the severity of the clinical situation and the judgement and experience of the treating physician.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm

Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one-to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 360 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use with Other Cardiovascular Agents

1. Sublingual NTG may be taken as required to abort acute anginal attacks during diltiazem therapy.
2. Prophylactic Nitrate Therapy: Diltiazem may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. Beta-blockers (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Diltiazem hydrochloride tablets, USP are available containing 30 mg, 60 mg, 90 mg or 120 mg of diltiazem hydrochloride.
The 30 mg tablets are white with a clear film-coat, unscored, round tablets debossed with **M** over **23** on one side and blank on the other side. They are available as follows:
NDC 0378-0023-01
bottles of 100 tablets
NDC 0378-0023-05
bottles of 500 tablets
The 60 mg tablets are white with a clear film-coat, scored, round tablets debossed with **M** over **45** on the unscored side. They are available as follows:
NDC 0378-0045-01
bottles of 100 tablets
NDC 0378-0045-05
bottles of 500 tablets
The 90 mg tablets are white with a clear film-coat, scored, capsule-shaped tablets debossed with **M135** on the unscored side. They are available as follows:
NDC 0378-0135-01
bottles of 100 tablets
NDC 0378-0135-05
bottles of 500 tablets
The 120 mg tablets are white with a clear film-coat, scored, capsule-shaped tablets debossed with **M525** on the unscored side. They are available as follows:
NDC 0378-0525-01
bottles of 100 tablets

Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]
Protect from light.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
REVISED JANUARY 2005
DILT:R7AQ